24 | JAPANESE ENCEPHALITIS VIRUS

24.1 | Disease agent

- Japanese encephalitis virus (JEV)

24.2 | Disease agent characteristics

- Family: *Flaviviridae*; Genus: *Flavivirus*; prototype virus of the JEV antigenic serocomplex.
- Virion morphology and size: Enveloped, icosahedral nucleocapsid symmetry, spherical particles, 40–60 nm in diameter.
- Nucleic acid: Linear, positive-sense, single-stranded RNA genome, ~11.0 kb in length.
- There are at least five distinct JEV genotypes (I-V) with genotype V being the most divergent. Genotypes I and III are largely in epidemic regions while genotypes II and IV are associated with endemic transmission.
- Physicochemical properties: Inactivated by heating for 10 min at >56°C; half-life of 7 h at 37°C; sensitive to treatment with lipid solvents, detergents, ether, trypsin, chloroform, formaldehyde, and β-propiolactone; infectivity reduced after exposure to irradiation and inactivated at pH 1–3.

24.3 | Disease names

- Japanese encephalitis (JE)

24.4 | Priority level

- Scientific/Epidemiologic evidence regarding blood safety: Moderate; transfusion transmission of JEV has been documented. Transfusion risk during JEV outbreaks exists.
- Public perception and/or regulatory concern regarding blood safety: Absent in nonendemic areas. Moderate in endemic areas and during epidemics.
- Public concern regarding disease agent: Absent in nonendemic areas. Moderate/high in endemic areas and during epidemics.

24.5 | Background

- Recognized in horses and humans in 1871; severe epidemic occurred in Japan in 1924; isolated from human brain in 1935.
- More than 3 billion people are believed to be at risk for JEV infection worldwide.
  - 24 countries in the WHO South-East Asia and Western Pacific regions have endemic JEV transmission.
  - Increasing in India, Nepal, and Southeast Asia while declining in Japan, S. Korea, Taiwan, and China since 1970 because of widespread vaccination programs and other preventive measures. Most recently detected in Pakistan, Papua New Guinea, and Australia.
  - Approximately 68,000 clinical cases with 13,600–20,400 deaths are estimated to occur annually.
  - The case fatality rate ranges from 5% to 30%.
  - Approximately 30%–50% of the surviving patients have permanent neuropsychiatric sequelae and complete recovery occurs in only one-third of patients.

24.6 | Common human exposure routes

- Vector-borne (primarily *Culex* mosquitoes around rice fields and stagnant water)

24.7 | Likelihood of secondary transmission

- Absent except for rare intrauterine transmission

24.8 | At-risk populations

- Widely distributed in Asia; emerging in Papua New Guinea and Australia
- Affects all ages, but especially children and the elderly

24.9 | Vector and reservoir involved

- Main epidemic JEV vectors are mosquitoes of the *Culex* species, especially *C. tritaeniorhynchus*, which is an evening- and nighttime-biting mosquito that feed preferentially on pigs and waterbirds (e.g., egrets and herons and sometimes ducks) as effective amplifying hosts. Humans and other vertebrate animals are incidental or dead-end hosts because of their low level of viremia that is insufficient to infect mosquitoes.

24.10 | Blood phase

- Asymptomatic viremia is recognized for JEV but has not been well characterized for duration and magnitude.

24.11 | Survival/persistence in blood products

- Transfusion transmission of JEV has been documented.

24.12 | Transmission by blood transfusion

- A 2017 case report from Hong Kong described transfusion transmission of JEV from an asymptomatic viremic donor to two immunocompromised persons, one of whom developed severe encephalitis and the other with asymptomatic seroconversion.

24.13 | Cases/frequency in population

- JEV is widely distributed in Asia; infection rates may exceed 1% during periods of peak transmission, which usually occurs from June to November.
- Where vaccination programs are not in place, nearly all persons in endemic areas have been infected (antibody-positive) by young adulthood.
- Before 1973, >300 cases of JE were reported among soldiers from the US, the United Kingdom, Australia, and Russia. From 1973 through 2017, 84 JE cases among travelers or expatriates from nonendemic countries were published or reported to the US CDC.
- From the time a JE vaccine became available in the United States in 1993, through 2017, only 12 JE cases among US travelers were reported to CDC.

24.14 | Incubation period

- 4–14 days from exposure to onset of symptoms

24.15 | Likelihood of clinical disease

- Most JEV infections are asymptomatic or mild (fever and headache), but approximately 1 in 250 infections result in severe clinical disease. Case fatality rate can be as high as 30% among those with severe disease symptoms.

24.16 | Primary disease symptoms

- Febrile headache syndrome.
- Aseptic meningitis.
- Encephalitis characterized by rapid onset with a 2–4-day prodrome of headache, fever, chills, nausea, vomiting, dizziness, and drowsiness followed by nuchal rigidity, photophobia, altered states of consciousness, seizures, hyperexcitability, and focal neurologic signs of CNS involvement.
- Acute flaccid paralysis similar to poliomyelitis can occur.

24.17 | Severity of clinical disease

- Severe manifestations of JE can occur with accompanying mortality. For those who survive, neurologic sequelae are frequent (45%–70% of JE survivors) often with thalamic or other lesions on MRI. Of survivors, 20%–30% suffer permanent intellectual, behavioral, or neurological sequelae such as a Parkinsonian syndrome, convulsive disorders, recurrent seizures, paralysis, mental retardation, psychiatric disorders and the inability to speak

24.18 | Mortality

- Ranges from 5% to 40% (2%–11% reported in US military personnel)
- Children and the elderly are at the highest risk for JEV mortality, with the highest frequency associated with poor medical care.

24.19 | Chronic carriage

- Evidence for persistent/latent infection in humans is based on recovery of JEV from peripheral blood mononuclear cells of asymptomatic children 9 months after acute JEV as well as in children developing recurrent disease. JEV also was recovered from cerebrospinal fluid 4 months after onset of symptoms.

24.20 | Treatment available/efficacious

- Supportive; no specific anti-viral treatment is available

24.21 | Agent-specific screening question(s)

- No specific question is in use.
- No sensitive or specific question is feasible.

24.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening tests exist for JEV.
- JEV can occasionally be isolated in cell culture from the blood of symptomatic cases with recovery up to one-third of cases from CSF.
- Serology on paired serum samples showing four-fold rise in titer by neutralization, complement fixation and/or hemagglutination inhibition are diagnostic.
- IgM-capture enzyme immunoassays are used for diagnosing JEV from serum and CSF.
- NAT and viral sequencing are used for evaluation of patients.

24.23 | Currently recommended donor deferral period

- No FDA Guidance or AABB Standard exists.
- Prudent practice would be to defer for 1 year after resolution of symptoms based on limited data regarding persistence in PBMC.

24.24 | Impact on blood availability

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

24.25 | Impact on blood safety

- Agent-specific screening question(s): Not applicable
- Laboratory test(s) available: Not applicable

24.26 | Leukoreduction efficacy

- Unknown

24.27 | Pathogen reduction efficacy for plasma derivatives

- Multiple pathogen reduction steps used in the fractionation process have been shown to be robust in removal of enveloped viruses.

24.28 | Other prevention measures

- One JE vaccine is licensed and available in the United States—an inactivated Vero cell culture–derived vaccine, Ixiaro, was approved in 2009 for use in people aged ≥17 years, then in 2013 for children 2 months through 16 years.
  - Clinical efficacy studies are not available for the US vaccine, whose approval was granted based on very high rates of induction of neutralizing antibody (96%–100%) in immunogenicity studies.
  - Because of reactogenicity, JE vaccine is not recommended for travelers with very low-risk itineraries, such as shorter-term travel limited to urban areas or travel that occurs outside a well-defined JE virus transmission season.
  - Other inactivated and live attenuated JE vaccines are used elsewhere but are not licensed for use in the United States.
- Mosquito control and avoidance.
- Flaviviruses are inactivated by multiple pathogen reduction processes that are available or in development for labile components.

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